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Running title

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Abstract

Ocular candidiasis is a major complication of Candida bloodstream infection (BSI). This study was performed to reveal clinical characteristics of ocular candidiasis. Of the 220 patients with Candida BSI, 204 cases received ophthalmology consultations between January 2005 and December 2011 at two teaching hospitals. Fifty-four (26.5%) cases had findings consistent with the diagnosis of ocular candidiasis. Of these 54 cases, 43 (79.6%) were diagnosed within 7 days after a positive blood culture. Among ocular candidiasis cases, more cases were due to *Candida albicans* (P = 0.034 OR; 3.68 95% CI 1.11-12.2) and had higher beta-D-glucan values (P = 0.001 OR; 9.99 95% CI 2.60 - 21.3). We need to consider fundoscopic examination to be performed within first 7 days of therapy, especially for those patients who have *C. albicans* BSIs and higher beta-D-glucan values. Additionally, follow-up fundoscopic examination should be considered before stopping therapy for high-risk patients.

Introduction

Bloodstream infections (BSIs) caused by *Candida* species have been reported to be increasingly frequent in recent decades, possibly due to rapid changes in medical practice. *Candida* BSI can lead to hematogenous dissemination and metastatic ocular infection with potentially devastating consequences. Consequently, a rise in related mortality and prolonged hospitalisation has been reported [Edmond et al., 1999; Jarvis et al., 1995; Kao et al., 1999; Pfaller and Diekema, 2007; Rentz et al., 1998; Sheng et al., 2005; Wisplinghoff et al., 2004].

Normally, patients who have chorioretinitis alone are often asymptomatic and respond better to systemic antifungal therapy than those with vitreal involvement. However, in advanced stages, the intravitreal injection of an antifungal agent with or without vitrectomy is needed. Thus, it is very important for doctors to properly diagnose ocular candidiasis in the early stages of the infection.

In this study, patients with blood cultures positive for *Candida* BSIs were reviewed for the incidence and clinical characteristics of ocular candidiasis to reveal the risk factors of

ocular candidiasis.

Materials and Methods

Study design

This study was performed at two teaching hospitals in Kyoto, Japan. Kyoto University Hospital (KUH) is a tertiary care university hospital with 1240 beds, and Katsura Hospital is an emergency hospital with 585 beds. Infectious disease physicians perform proactive interventions for all patients with BSI in these hospitals. In cases of *Candida* BSIs, catheter removal is recommended, blood cultures are collected to confirm all negative results, and finally, fundoscopy is performed by ophthalmologists usually within first 7 days of therapy. *Candida* BSI was defined by at least one positive blood culture for *Candida* species and a clinical sign of infection (e.g., fever, hypotension or tachypnea).

Two hundred and twenty cases of *Candida* BSIs were diagnosed in the two Kyoto teaching hospitals from January 2005 to December 2011. To assess the incidence and clinical characteristics of patients with ocular involvement, we performed medical chart reviews of the *Candida* BSI patients who had

consulted ophthalmologists. For the classification of ocular candidiasis, we incorporated the criteria proposed by Oude Lashof [Oude Lashof et al., 2011]. Proven ocular candidiasis was defined as ocular lesions in combination with positive histology or a positive culture of a vitreous aspirate. Probable *Candida* endophthalmitis was defined as vitritis or fluffy lesions with extensions into the vitreous humour. Probable *Candida* chorioretinitis was defined as deep focal white infiltrates in the retina. If signs of chorioretinitis were observed in patients with an underlying systemic disease that reportedly exhibits similar lesions (e.g., diabetes, hypertension or concomitant bacteremia), these cases were classified as possible ocular candidiasis.

Clinical information acquired from medical charts included age, sex, underlying diseases, receipt of corticosteroids or other immunosuppressive agents during the previous 30 days, any antimicrobial therapy during the previous 30 days, surgery during the previous 30 days, time to first negative blood culture, interval between blood culture and antifungal therapy, interval between sign of infection and removal of the catheter or antifungal agents, interval between positive fungal culture and

catheter removal, the specific fungal species, antifungal therapy and 30-day mortality. Digestive tract involvement included any gastrointestinal disorders such as malignancies of digestive tract and inflammatory bowel diseases. The (1,3)-ß-D-glucan (BDG) test values that were taken within 3 days after positive blood cultures were also evaluated. At Katsura, the BDG values were determined using the Fungitec G test (Seikagaku Corporation, Tokyo, Japan). At KUH, the BDG values were determined using the WAKO ß-glucan test (Wako Pure Chemical Industries, Tokyo, Japan). The results were analysed according to the manufacturer's instructions.

Statistical analysis

Categorical variables were compared using Fisher's exact test. Continuous variables were compared using the Kruskal-Wallis test or the Mann-Whitney U test. BDG values under the limit of detection were considered to be 0.0 pg/mL. Receiver-operating characteristic (ROC) curves for the BDG levels were constructed, and their optimal cut-off values were determined with the maximum Youden index. Potential factors associated with ocular candidiasis were examined by Cox proportional hazards

regression analysis. All covariates with a *p*-value of less than 0.10 on univariate analyses were subjected to further selection by the above-mentioned multivariate analyses. The data were analysed with PASW software version 18.0 (SPSS) for Microsoft Windows. All P value tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Incidence

Of the 220 patients with *Candida* BSI, 204 presented to ophthalmologists for the diagnosis of ocular candidiasis were included in this study. Six of the 16 *Candida* BSI patients who did not consult ophthalmologists included critically ill patients whose prognosis had been presumed to be very poor or who died before the identification of positive fungal cultures.

Fifty-four (26.5%) of the 204 *Candida* BSI patients who were evaluated by ophthalmologists had fundoscopic abnormalities that met the criteria for ocular candidiasis. Among ocular candidiasis cases, 10 were probable endophthalmitis, 24 were probable chorioretinitis, and 20 cases were possible

chorioretinitis.

Epidemiologic characteristics

The baseline characteristics of the study population are shown in Table 1. The groups with or without ocular involvement did not differ with respect to age, sex, diabetes mellitus status, the use of immunosuppressive agents or the use of systemic antibiotics within the previous month, but more patients with ocular involvement had malignancies. In addition, more patients with ocular manifestations had digestive tract abnormalities (e.g., digestive tract surgery, inflammatory bowel syndromes, malignancy of a digestive tract), whereas ocular candidiasis was rare in the departments of Dermatology, Rheumatology and Cardiovascular Surgery. Ocular candidiasis patients were infected significantly more frequently with *Candida albicans* and less often with *C. parapsilosis* than patients without retinal lesions. The length of time to the first negative blood culture, the time to catheter removal and the administration of antifungal agents did not differ between groups.

Timing of fundscopic examination

One hundred and eighty (88.2%) patients received fundscopic

examination once and 24 patients received twice or more. Ocular abnormalities consistent with ocular candidiasis were diagnosed within 7 days after positive blood culture in 43 patients, whereas 11 patients were diagnosed as having ocular candidiasis more than 8 days later (Figure 1). Twenty-one (38.9%) patients were diagnosed within 3 days, and the average time from a positive blood culture to the diagnosis of ocular candidiasis was 5.5 days. The time to the first negative fungal culture was longer in the patients who were diagnosed with ocular candidiasis at the time of a second fundoscopy performed more than 8 days later after the positive fungal culture; all patients had malignancies, had diabetes mellitus or were being treated with immunosuppressive agents.

BDG values and ocular candidiasis

The diagnostic kit used for the measurement of BDG values differed between KUH and Katsura; therefore, we created ROC curves and determined that the appropriate cut-off values were 22.5 and 42.7 for KUH and Katsura, respectively. A case was defined as BDG-high if the BDG value was higher than the cut-off value. Using the cut-off value, more patients with ocular

candidiasis than patients with non-ocular candidiasis were grouped as BDG-high cases. There was no relationship between the BDG value and causative agents (data not shown).

Clinical outcome

Among 54 cases of ocular candidiasis, 42 patients completed antifungal therapy without any worsening of visual acuity, and 12 patients died before the completion of antifungal therapy. Among the chorioretinitis cases, 33 out of 35 patients who provided a report indicated they had no ocular abnormalities. Among the ocular candidiasis cases, micafungin was prescribed to 23 patients, and fluconazole was prescribed to 25 patients. In 16 of the 23 patients who received micafungin therapy, the antifungal treatment regimen was shifted to fluconazole or amphotericin-B after the diagnosis of ocular candidiasis. The 30-day mortality rate of patients with ocular abnormalities was also higher, although these differences were not statistically significant.

Analysis of risk factors

Candida albicans as the etiological agent (P = 0.034 OR; 3.68 95% CI 1.11-12.2) and higher beta-D-glucan values (P = 0.001 OR; 9.99

95% CI 2.60 – 21.3) were statistically significant for the risk factors of ocular candidiasis, as determined by multivariate regression analysis (Table 2).

Discussion

This study investigated the incidence and clinical characteristics of ocular candidiasis. According to previous studies, the prevalence of ocular candidiasis is estimated to be between 1 - 45% [Rodrguez-Adria´n et al., 2003; Oude Lashof et al., 2011, Parke et al., 1982; Brooks, 1989; Shah et al., 2008]. In this study, ocular abnormalities occurred in 26% of 204 patients. It is likely that patient selection led to the comparatively high prevalence of ocular candidiasis. Among our patients, 50% had malignancies, and more than 80% had predisposing risk factors such as antibiotic exposure, diabetes mellitus or the use of immunosuppressive therapy. Furthermore, many patients had been admitted for gastrointestinal diseases. Malignancy and gastrointestinal disease were statistically significant risk factors for ocular candidiasis as determined by chi-squared tests, although the statistical significance was not retained in the

multivariate regression model. Considering the pathogenesis of endogenous ocular candidiasis, physical mucosal damage and changes in normal flora induced by broad-spectrum antibiotics or chemotherapy may facilitate the occurrence of ocular involvement. Thus, the high prevalence of ocular candidiasis observed in this study may have been the result of the severely immunocompromised state of many patients.

Of all of the *Candida* species, *C. albicans* was observed to have the greatest propensity to cause ocular candidiasis. In contrast, *C. parapsilosis* was associated with ocular manifestations significantly less frequently. In this study, patients with ocular candidiasis were mostly infected with *C. albicans,* a finding that is consistent with prior reports (Donahue et al., 1994; Rodrguez-Adria´n et al., 2003; Oude Lashof et al., 2011, Parke et al., 1982; Brooks, 1989; Shah et al., 2008). Some of these cases occurred despite prompt catheter removal and the immediate administration of antifungal agents after the onset of *Candida* BSIs. These results suggest that fungal virulence as well as host and treatment factors may be involved in the pathogenesis of ocular candidiasis. It is likely that the high

prevalence of *C. albicans* may also have increased the rate of ocular candidiasis in this study.

Several studies revealed that the prospective evaluation of circulating BDG in high-risk patients generates positive results that are available before the culture results and can improve the diagnosis of invasive candidiasis (Koo et al., 2009; Acosta et al., 2011; Ostrosky-Zeichner et al., 2005). In this study, more patients with ocular candidiasis had higher BDG values, and BDG positivity had a significant relationship with the development of ocular candidiasis. However, there was no relationship between elevated BDG values and etiologic agents such as *C. albicans* or the prognosis of *Candida* BSIs (data not shown). Although the BDG values that reflect the burden of *Candida* species and the half-life are still unknown, when higher BDG values are present, ocular candidiasis may have already occurred in these patients, even if they are asymptomatic.

Despite the high prevalence of ocular candidiasis, periodic ophthalmologic examinations are rarely performed in patients susceptible to opportunistic infection. According to the IDSA guidelines for invasive candidiasis, ophthalmologists should

investigate each patient for the presence of ocular candidiasis (Pappas et al., 2009), but the optimal timing for this evaluation has not been established. Previous studies have advised an interval of < 14 days between the start of treatment and the first retinal abnormality, an interval that is consistent with candidal chorioretinitis (Rodrguez-Adria´n et al., 2003; Krishna et al., 2000). Although the optimal treatment for endogenous ocular candidiasis has not been clearly established yet, fluconazole and voriconazole appear to be the most effective (pappas et al., 2009; Khan et al., 2007). In our study, 80% of cases were diagnosed within 7 days, and the antifungal agents were changed from micafungin to azoles or amphotericin in 16 of the 42 ocular candidiasis cases. If fundoscopy was performed later, the opportunity for the earlier administration of potentially more optimal antifungal agents might have been missed. In our study, more than 80% of the ocular candidiasis cases were chorioretinitis, which usually does not require surgical interventions. Many patients completed the course of antifungal therapy without any visual disturbance. We speculate that earlier diagnosis and treatment resulted in the improved prognosis regarding visual

acuity. On the other hand, some ocular candidiasis cases were diagnosed by a second fundoscopic examination more than 8 days later. Ideally, when we consider a strategy based on the fact that earlier diagnosis yields a better prognosis, fundoscopic examination should be performed within first 7 days of antifungal therapy, especially in those with *C. albicans* BSIs and higher BDG values. In addition, follow-up fundoscopic examination should also be considered in severely immunosuppressed patients, even if the first fundoscopic examination yielded negative results.

Study limitations

This study has several limitations, including the fact that most of the patients without ocular candidiasis were not re-examined serially. Conceivably, the disseminated fungal lesions could have arisen in healthy eyes after the initial exam and therefore may have been missed in some cases. Second, approximately 7.2% of the *Candida* BSI patients did not consult ophthalmologists for their underlying conditions. During discussion with those patients about the risk factors for ocular candidiasis, fundoscopy may have been indicated but not performed in some cases.

Thirdly, we included the possible cases of ocular candidiasis who had severe underlying diseases in this study. The prevalence rate of ocular candidiasis might have been much lower than reported here.

Transparency Declaration

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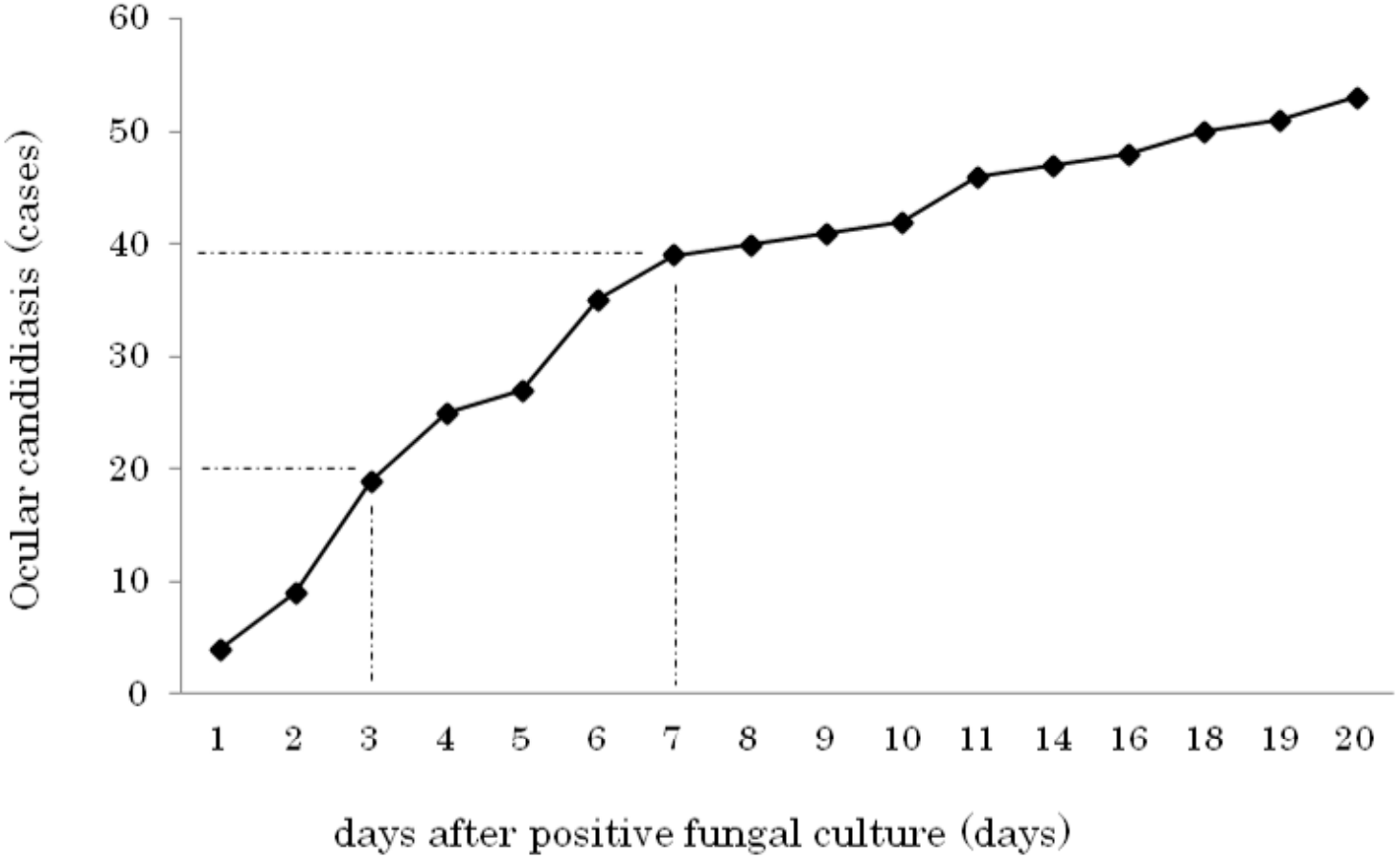
Figure 1 Cumulative incidence of ocular candidiasis

Ocular candidiasis was diagnosed within 7 days after positive blood culture in 43 patients, whereas 11 patients were diagnosed with ocular candidiasis more than 8 days later.

Figure 1


Ocular candidiasis (cases)
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
14
16
18
19
20
days after positive fungal culture (days)

1 Table 1 Clinical characteristics of the study patients

	Ocular candidiasis (N=54)	(%)	Non-ocular candidiasis (N=150)	(%)	*P*
Age	62.8 ± 18.9		63.14 ± 19.8		0.923
Male	28	51.9%	80	53.3%	0.875
Malignancy	41	75.9%	60	40.0%	<0.001
Diabetes mellitus	12	28.6%	22	17.3%	0.210
Digestive tract involvement	35	68.6%	61	41.5%	0.001
Immunosuppressive agent	20	37.0%	32	21.3%	0.083
Antibiotic within one month	46	86.8%	112	74.7%	0.083
Surgery within one month	17	31.5%	46	30.7%	0.911
C. parapsilosis	3	5.6%	35	23.3%	0.002
C. albicans	40	74.1%	67	44.7%	<0.001
C. glabrata	5	9.3%	19	12.7%	0.626
C. tropicalis	5	9.3%	18	12.0%	0.862
High beta-D-glucan (N=88)	29	74.4%	31	34.4%	<0.001
Time to first negative blood culture, mean, range (days)	5.52 ± 4.04, 1-14		5.32 ± 3.40, 1-27		0.787
Blood culture to antifungal agent, mean, range (days)	1.82 ± 1.37, 1-5		2.34 ± 2.81, 1-5		0.117
First sign of infection to removal of the catheter,	1.52 ± 2.30, 1-12		1.56 ± 2.17, 1-11		0.920

mean, range (days)					
Sign of infection to antifungal agents, mean, range (days)	2.28 ± 3.17, 1-8		2.36 ± 2.53, 1-9		0.872
Interval between positive fungal culture and catheter removal, mean, range (days)	1.00 ± 3.99, 1-3		0.72 ± 1.82, 1-3		0.647
30-day mortality	14	25.9%	28	18.7%	0.326

2

Table 2 Results of multilvariate regression analysis of factors associated with ocular candidiasis

	P value	Exp(B)	95% CI
(1,3)-β-D-glucan high	0.001	9.99	2.60-21.3
C. albicans	0.034	3.68	1.11-12.2
Digestive tract involvement	0.290		
Malignancy	0.714		
Immunosuppressive agent	0.625		
Antibiotic within one month	0.483		